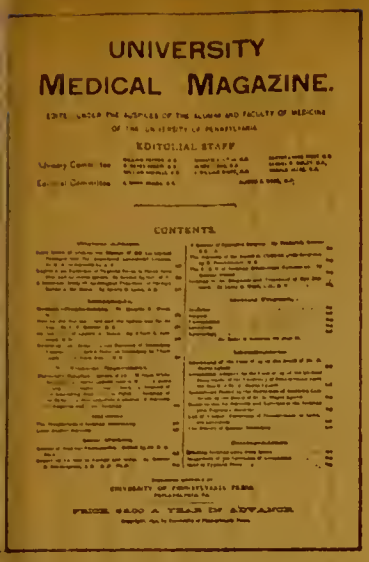
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CONTENTS

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THE ELIMINATION OF ETHER AND ITS RELATION TO THE KIDNEY.

BY GEORGE B. WOOD, M.D.

THE ELIMINATION OF ETHER AND ITS RELATION TO THE KIDNEY.[1]

By George B. Wood, M.D.

It has been the teaching of the leading medical authorities of this country and abroad that the elimination of ether is accomplished by the kidneys and the lungs. I do not think, however, that it has ever been conclusively proved that the kidneys do excrete ether. Yet it seems, *a priori*, very probable that if ether exists in the blood in the free state the kidneys will attempt to rid the body of it. The existence of ether in the blood during anesthesia has never been doubted, but I have thought it would be worth while to positively determine whether this is so by the following experiments:

Experiment II.—Killed dog after thirty minutes' inhalation of ether. Blood was allowed to flow from the jugular vein through cannula and rubber tube into a narrow-neck glass flask, which was tightly corked as soon as the blood was drawn. This blood smelt very strongly of ether, and was further tested in the following manner: NaOH was added to blood to keep it in solution while it was being distilled over a water-bath. The resulting distillate smelt of ether and gave a slight reaction to the following test: Put a few fibres of asbestos in a test-tube and add potassium chromate and sulphuric acid; the solution containing ether is now added, and a color varying from a yellowish-green to a true blue, according to the amount of ether present, is observed. I think this experiment proves conclusively the existence of free ether in the blood.

We now come to the more important point, that of the elimination of ether by the kidneys. The conclusive proof of this action would be the finding of ether in the urine, and it was with this end in view that I examined urine from patients who had been etherized.

Before giving the results of these examinations, I would like to call attention to the means of detecting ether in the urine. There are practically only two ways in which this can be accomplished: first, by the odor; second, by H_2SO_4 and $K_2Cr\,O_4$ test. The first is by far the simplest and most delicate.

I have proved by repeated trials by myself and by others that if one drop of ether be added to two or three ounces of urine and placed

[1] Isaac Ott Prize Thesis, University of Pennsylvania, 1894.

in an open beaker, its odor can be perceived twenty minutes afterwards. Of course, the odor by that time has become very slight, and if the urine be allowed to stand will disappear altogether. The other test is not nearly so good, and it can only be practised on the distillate of the urine, as the charring effects of the H_2SO_4 on the organic substances of the urine entirely cloud over any reaction which might take place. In distilling for ether the urine should be kept from 120° to 180° F., so as to avoid distilling too much water over into the receiver. The receiver should be surrounded with cracked ice, so as to increase the concentration of the ether vapor. The distillate is then tested for ether as in Experiment II.

In the following examinations I trusted entirely to the sense of smell for the detection of ether. The urine was from patients who had been etherized in the University Hospital. The urine was always the first voided after the etherization. Where a question-mark is placed in the "result" column, it means that it was impossible to determine whether a suspicious smell was that of ether or that of a urinous principle:

No.	Result. Distilled.	Length of Etherization.	Amount Passed.	Time after Etherization.
I	No odor.	1 hour.	. . . .	
II	"	30 min.	. . . .	
III	"	. . . . .	9 oz.	6 hours.
IV	"	. . . . .	. . . .	3 "
V	"	. . . . .	6 "	14 "
VI	"	. . . . .	8 "	6 "
VII	"	. . . . .	10 "	6 "
VIII	Odor of ether distinctly perceivable; disappeared on boiling; distillate smelt of ether.	15 min.	7 "	3 "
IX	No odor.	45 min.	10 "	9 "
X	"	30 min.	4 "	7 hrs. 30 min.
XI	"	30 min.	3 "	5 hrs. 30 min.
XII	"	. . . . .	4 "	6 hours.
XIII	?	. . . . .	6 "	5 "
XIV	?	. . . . .	3 "	3 "
XV	?	. . . . .	8 "	
XVI	?	1½ hrs.	6 "	

In Number 8, there was a possible source of error, viz.: the bottle in which the urine was put had once contained ether, and enough of it had possibly been left in to taint the urine.

The average amount of ether used in these experiments was about eight ounces. As one drop of ether may be detected in two or three ounces of urine, and as not in a single instance (with the exception of

Number 8) was there positive odor of ether, it seems very certain that if ether escapes through the kidneys at all it must be only in the minutest quantity.

What, then, is the fate of ether? It differs very little in its chemical composition from alcohol, and it might seem as though there would be some relation between the two in regard to their elimination. Alcohol, as we know, is partly eliminated by the kidneys and partly by the lungs; and is partly destroyed in the system. Ether, as has been shown, is not excreted by the kidneys. The destruction of ether in the body cannot be so great as that of alcohol, because ether, which is the oxide of ethyl, is a much more stable compound than alcohol, the hydrate of ethyl. Yet I think ether may to some extent undergo decomposition. But for the chief elimination of ether we must look to the lungs, for the odor of ether is distinctly perceivable on a patient's breath many hours after the operation, and it seems most natural that the lung should give forth that which it has taken in.

If ether be not eliminated by the kidneys, why is it that clinically we find following anesthesia many cases showing renal irritation? The suggestions of this question led me to make a series of experiments on the dog. In these experiments ether was always given by inhalation. Dr. Guitéras kindly went over the slides presented with this paper, and confirmed the statements hereafter made.

Experiment I.—3.12, started to administer ether.

3.20, nozzle of canula with a rubber tube attached was put into carotid.

3.40, clip was taken off artery, and dog bled between one and two pints, which was collected in a glass flask.

3.50, killed dog with chloroform; dog dead two minutes after chloroform was started.

This experiment was started with the intention of proving the existence of free ether in the blood. So far it was a failure, for, as afterwards discovered, the flask used was one in which petroleum ether had been kept. Post-mortem showed the cortex of the kidneys to be slightly congested, while medulla was of a normal color. Pieces from the cortex were hardened in a saturated solution of $HgCl_2$, with equal parts of alcohol and water. Having been left in this solution for twenty-four hours, they were washed in water and put through graduated alcohol up to absolute, and then embedded in colloidin. (This is the process of hardening used in all the experiments except where otherwise indicated.) Microscopical examination showed distinct cloudy swelling of the proximal convoluted tubules. The tufts and discharging tubules were not affected. The nuclei of convoluted tubules were generally well stained, only here and there refusing to take the stain.

There enters into this experiment the possibility that the bleeding and the chloroform inhalation caused the parenchymatous degeneration, but as they came so near the death of the animal, it hardly seems possible that sufficient time elapsed for this to have caused the change. But, to be sure, I made the following experiment with the sole purpose of determining whether ether was capable of causing cloudy swelling in the kidneys or not.

Experiment III.—12.05, ether inhalation commenced.

1.50, killed dog with ether.

The post-mortem showed the kidneys to be deeply congested. The congestion seemed to be limited to the cortex, the medullary substance being of an almost normal color. Microscopical examination: Blood-vessels were universally congested. This was true of the medulla as well as the cortex. The capillaries of the glomeruli were distended even to rupture in a couple of instances. The cloudy swelling in this case was very irregular, in some tubules being very well marked, while in others it was only slightly so.

The results of these two experiments are confirmed by all the rest of the series, cloudy swelling existing in all to a greater or less extent. This appears to me to prove that it is possible with one inhalation to produce a change in the normal status of the kidney.

It might seem to some as though this cloudy appearance might only be a temporary activity of the kidney, due to the intense congestion, and not a true parenchymatous degeneration. It is difficult to say just where the granular appearance of an active cell leaves off and where the more opaque effect of cloudy swelling begins, but the following experiment shows that the change is something more than a mere temporary affair of a few hours, entirely dependent on the congestion.

Experiment XVI.—10.00 A.M., commenced ether.

11.15 A.M., stopped ether. (Dog recovered consciousness.)

5.30 P.M., killed dog by pitting.

The post-mortem showed the kidneys to be of a normal color, only the slightest apparent trace of congestion in the edge of the cortex next to the medullary substance. Microscopical examination: Distinct cloudy swelling, being no less marked than in some dogs killed immediately after etherization.

Though the congestion had for all practical purposes disappeared, this clouded state still continued. I think we must acknowledge that ether is the active agent which causes both the congestion and the parenchymatous degeneration.

Yet how can ether be irritative to the kidneys when it is not excreted by them? As ether exists in the blood, it must of necessity go into the smallest capillaries over the whole body, and it seems pos-

sible that its action could be made manifest even through the walls. We see that in several instances the liver-cells show a slight cloudy swelling (see Experiments V and XII), and it is highly probable that all the tissues of the body come more or less in contact with it, but would only show alteration in their structure in so far as they are irritated by it. The kidneys, being more sensitive to its influence than any other tissue, would consequently show more change. It is also possible that there is an attempt at the elimination of ether, but that it is so irritative to the cells that they are unable to excrete it.

It has occurred to me that if ether caused such a decided effect in so short a time, a more lengthy exposure would produce a yet more pronounced alteration, and for this purpose I made a couple of experiments.

Experiment V.—October 19, etherized for one hour.

October 20, etherized for one hour.

October 21, etherized for one hour.

October 23, etherized for seventeen minutes.

On October 23, killed the dog after seventeen minutes' etherization. He seemed to have polyuria. The post-mortem showed kidneys to be deeply congested, the congestion extending to some extent down into the medullary substance. These kidneys showed the peculiar macroscopical appearance of cloudy swelling. Microscopic examination: The whole kidney showed more or less cloudy swelling, the straight tubules and glomeruli being affected as well as the convoluted tubules. Some parts of the convoluted tubules were greatly affected, while other portions were only slightly so. Evidence of some slight desquamation was seen in the granular matter which had collected in the lumen of the collecting tubules. Pieces of the liver were in this case saved, and on examination showed swollen cells and some cloudy swelling, but the nuclei generally were well stained.

Experiment XI.—November 6, etherized for one hour.

November 7, etherized for one hour.

November 8, etherized for one hour.

November 9, etherized for thirty minutes.

This dog had a weak heart, and when he died it stopped before the respiration did. The post-mortem showed a distinctly flabby heart. The kidneys were congested. Microscopic examination: Kidneys showed cloudy swelling well marked in convoluted tubules. It extended to the epithelium of the glomeruli, and also down into the straight tubules.

These repeated etherizations seemed rather to make more general the disturbance of the kidneys than to cause a more intense inflammation. Yet Experiment V shows a tendency towards desquamation,

indicating that if the cloudy swelling were kept up day after day, the tubules would discharge diseased cells.

The summary of this whole matter is, that ether is a decided irritant to the kidneys, capable of causing a true parenchymatous degeneration of that organ, even when in a healthy state. The clinical application of this is very simple. If the kidney be a healthy one the action of ether on it does not amount to much ; but if the kidney be at all diseased ether should be administered only with the greatest care, lest its irritative influence tend to greatly increase the disease processes.

When fully developed uremia exists it would be absurd to attempt etherization, for the centres of respiration, already carrying as heavy a load of uremic poison as they can, would give way completely when the extra strain of the depressing action of ether was felt. Of course, when the above circumstances exist, no one, after a moment's thought, would think of giving ether ; but let us suppose a case to be in the earlier stages of kidney disease, when probably the uremic poison was just commencing to accumulate ; under such circumstances would a surgeon be justified in administering ether in an operation which was important enough to cause him to pass by the local effects of the drug ?

This, of course, depends on how soon the respiratory centres begin to feel the influence of the uremic poison. With this thought in mind I made another series of experiments. The idea was to have two dogs, one with diseased kidneys, and the other with healthy kidneys, under such circumstances that they would both receive their proportionate share of ether. For this purpose I made a tank large enough to accommodate two dogs, with a partition in the middle to keep them separated. The top was made of glass so they could easily be observed. After the dogs were put in the tank, and the lid was fastened down with thumb-screws, ether was sprayed into the tank through a hole. It took from eight to ten minutes for the dogs to become unconscious. Generally there was considerable excitement, but sometimes they would lie down and quietly go to sleep. By means of this tank two dogs were in the same atmosphere of ether at the same time, and, consequently, getting their proportionate share of ether.

For the purpose of producing nephritis I employed the tincture of cantharides in doses varying from five drops to one drachm, three times a day, according as the dog showed irritation of the kidneys. The first dog I tried had albumin and granular tube-casts in his urine when he had only received twenty-four drops. All the other dogs that I tried seemed to have kidneys made of leather, as far as cantharides was concerned, showing no signs of nephritis even when taking a drachm a day.

Unfortunately, I had not my tank ready when the first dog showed albumin in his urine, and both desiring to see the effects of ether on him, and supposing I could produce a like nephritis in another dog without any trouble, I gave him ether with the funnel, being in too big a hurry to wait. This was the following experiment.

Experiment IV.—This dog received in his food twenty-four drops of the tincture of cantharides between October 19 and 22. On October 23 I etherized the dog for thirty-five minutes. He had scarcely come under the influence of ether when his breathing ceased, but it started again after a few minutes of artificial respiration. The urine passed during the excitement stage was scanty, containing quite a large quantity of albumin and numerous tube-casts. On October 27 I etherized him again. At 10.35 commenced ether, and at 10.45 dog stopped breathing. Artificial respiration was of no avail. Urine again contained albumin and casts. The post-mortem showed commencing congestion on outer border of cortex of kidneys. Microscopic examination: Kidneys, the epithelial cells of the glomeruli, were desquamating, and in some places the tufts had dropped out, leaving only the capsule. Desquamation of the convoluted tubules was also noticed. There was cloudy swelling and some fatty degeneration. In one or two places karyokinetic figures were seen, and signs of cell-divisions frequently met with. The lung, liver, and spleen were normal.

The next experiment was on a supposed healthy dog, but post-mortem revealed kidney-disease secondary to bladder-disease.

Experiment X.—November 2, etherized for one hour.

November 3, etherized for fifteen minutes.

Death took place suddenly after a fresh quantity of ether had been put on the cone. The heart continued beating fully two minutes after respiration had ceased. This dog had an intense urethritis with a probable stricture, causing an enormously-distended bladder. Microscopic examination: Epithelial cells of the kidney were desquamated, but no signs of karyokinesis. It seemed as though the cells had been floated off. The nuclei took the stain perfectly well. Cloudy swelling extended all over the kidney. Congestion was intense, especially well marked at the periphery of the cortex. Some of the tufts were compressed and small.

These experiments show the effects of ether on the respiratory centres in cases of commencing nephritis, and I was in hopes of confirming these results by more exact experiments, but as I failed to produce another case of nephritis, and was not lucky enough to find one, no important facts were obtained. Nevertheless, I will briefly describe these later experiments, as they show some other important points.

Experiments VIII and XII.—Dog No. 8 received in his food

between October 28 and November 13, five fluid drachms and ten drops of the tincture of cantharides. On November 13 he had retention of urine. On the same day this dog, with a healthy one, No. 12, was put into the tank. Ether was started, and in one hour and two minutes No. 8 stopped breathing; seven minutes later, one hour and nine minutes, No. 12 stopped breathing. The post-mortem showed No. 12 to have congestion of both liver and kidneys. Microscopic examination: No. 8, kidneys,—a very general cloudy swelling was seen, the cell-walls disappearing; the lumen of the tubules seemed to be filled with granular matter; the capsule surrounding the tufts was swollen and showed hyaline change, but no cell proliferation; in one or two tubules the granular matter took the form of casts, yet there was no desquamation or karyokinetic figures; the liver showed marked fatty degeneration; this showed well as it was hardened in Flemming's solution. No. 12, kidney,—intense congestion of the cortex was noticed, also hemorrhage into several of the glomeruli; there was moderate cloudy swelling, but the nuclei with a few exceptions took stain well; the cells of the liver seemed to have undergone slight parenchymatous degeneration, and the whole organ was entirely congested.

Experiments IX and XIII.—Dog No. 9 received in his food, between October 28 and November 5, five fluid drachms and twenty drops of the tincture of cantharides. On November 6, No. 9, with a healthy dog, No. 13, was placed in the tank. (At this time No. 9 showed retention of urine which was thought to contain a trace of albumin.) No. 9 died after seventeen minutes' inhalation; No. 13 dying in thirty-three minutes. The post-mortem showed the kidneys of No. 13 to be congested, while those of No. 9 were scarcely so at all. Microscopic examination: in No. 9 there was varying degrees of cloudy swelling without any evidences of inflammation; the cloudy swelling was certainly not more marked than it was in some of the cases which had not taken cantharides. In No. 13 there was varying degrees of cloudy swelling, often obscuring the outlines of the cells, but the nuclei were generally well preserved.

Experiments XIV and XVII.—No. 14 received with his food, between November 15 and 25, eleven fluid drachms and twenty drops of the tincture of cantharides. No. 14, with his partner, No. 17, was put into the tank on November 27. No. 14 died in twenty-seven minutes, and No. 17 in thirty minutes. The post-mortem showed the kidneys of No. 17 to be very much congested, while those of No. 14 were only very slightly so. Microscopic examination: No. 14 showed moderate swelling; No. 17 showed less cloudy swelling than its partner, the outlines of the cells being better preserved.

In both of the experiments, IV and X, death took place accidentally

from failure of respiration, and in both cases there was more or less kidney-disease. These two experiments seem to back up very strongly my suggestion as regards the effect of ether on the respiratory centres in kidney-disease. Yet they do not prove anything, for they may only have been coincident, as every once in a while, in experimenting with dogs, one is apt to suddenly stop breathing and die ; but it may be that these occasional deaths are due to a nephritis. Therefore it is my belief that in case of nephritis surgeons should give ether only with the greatest care, continually watching for any signs of failure of respiration. An important point is that ether should be given very gradually, and when during the anesthesia it is necessary to use more ether, the inhaler should not at once be put directly on the face but brought gradually closer, the anesthetizer carefully watching the patient's breathing.

It is well, before I end this paper, to give a brief summary to bring out the chief points and facts obtained.

First, as regards the relation of ether to the healthy kidney. It has been proved that ether exists as such in the free state in the blood, and yet coming as it must in close relation with the kidney, it is, contrary to previous opinions, not excreted by that organ to any appreciable amount. Nevertheless, it has been demonstrated that in ether anesthesia the kidney becomes congested, and on microscopical examination the cells show cloudy swelling. The cells of the convoluted tubules are primarily affected, the tufts and collecting tubules only evincing change when the anesthesia had been prolonged. Repeated administrations of ether, if kept up long enough, would probably cause desquamation of the epithelial cells.

Second, as regards the diseased kidney. The local effect of ether must be very deleterious to an already diseased kidney, for any unhealthy organ will not stand wear and tear like a normal one. In cases where uremic poisoning was commencing to make itself apparent, it was shown that there existed a liability to sudden death during ether narcosis, due to the action of ether on the already depressed centres of respiration.


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